Lentz

Lentz discloses essentially the same **filtration** procedure as claimed by applicant, but with one major difference: Lentz discloses removal of all blood components of 200,000 mw or less. As a result, the patient loses all of their IgG and IgA antibodies, which are extremely important to fight infection. As the examiner is also aware, infection is a major problem for cancer patients, so the first method would not have been developed if the patentee had even remotely believed that one did not have to remove the immunoglobulins. However, it simply had not been determined even as of the issue date of the '713 patent (1987), what the active component was that was being removed by the procedure, which allowed the patient to then fight off the cancer. It has taken years of subsequent work to determine that the "bad" component which is removed by the procedure is a relatively low molecular weight component, allowing the substitution of a filter with a lower molecular weight cutoff.

There is absolutely no teaching in the '713 patent that would lead one of skill in the art to believe that a lower molecular weight cutoff could be used. It has been well established by the Courts that the reference(s) cited under §103 must not only disclose the elements applicant is claiming but the motivation to use them as applicant has done, with an expectation of success. That test cannot be met by the '713 patent. At col. 6, lines 34-46, Lentz specifically states that the **immunosuppressive element** "is believed to be an IgG type immunoglobulin molecule. The other fraction has a molecular weight between about 200,000 and 1,000,000 and is believed to be an immune complex." col. 6, lines 43-46. Accordingly, not only is there no disclosure of the claimed elements in Lentz, there are two specific statements **arguing the criticality of the higher molecular weight cutoff of the filter**, teaching away from what applicant has now developed. One skilled in the art would simply not practice the currently claimed method

because Lentz teaches that it would **not** be successful!

Chen

Chen teaches that soluble TNF-alpha receptors suppress the patients ability to fight cancers. As discussed above, Lentz teaches that something about the size of an immunoglobulin, or larger **(i.e., larger than 120,000 daltons)**, is instrumental in suppressing a patient's ability to fight a tumor. Soluble TNF-alpha receptors are 55,000 and 75,000 daltons in size (page 541, col. 1). The combination of Lentz with Chen is **not** the same as what applicant is claiming. Moreover, there is nothing that would lead one to believe that you could remove only the smaller molecular weight molecules and still effectively treat the cancer based on reading Lentz. Therefore, one skilled in the art would be led **away** from the combination of Lentz and Chen, **not** to a **modified combination**.

Wolpe

Wolpe does not make up for the deficiency of Lentz. Lentz clearly states that there is an immunosuppressive element of a molecular weight similar to that of an immunoglobulin or immunoglobulin complex **(i.e., greater than 120,000 daltons)** which must be removed for a patient to effectively fight the cancer. Wolpe states that certain factors are known which enhance the immune system. Wolpe does not address the issue of whether or not there is an immunosuppressive component having a molecular weight in the critical range between that which is now claimed and that which is taught in the thirteen year old patent to Lentz, prior to many subsequent studies which were required to determine that the immunosuppressive element does **not have a molecular weight similar to that of an immunoglobulin or immunoglobulin complex.** The difference is important: by using the lower molecular weight cutoff, the patient can keep their own immunoglobulin, helping them to more successfully fight off infection.

In summary, no where has the examiner provided any motivation as to why one of ordinary skill in the art would be led to change the filter device of Lentz to **exclude** the very molecules he says must be removed for the treatment to be effective. No art has been cited which would provide the motivation to specifically remove soluble cytokine receptors using such a device or column. No art has been cited that would motivate one skilled in the art to make the specifically claimed combinations of treatments to remove low molecular weight components in combination with a treatment such as thalidomide. It is well established that it is not enough to cite individual references that disclose claimed elements: the prior art **must**

disclose each element,

lead one skilled in the art to combine the elements as applicants have done,

with a reasonable expectation of success.

To go to the FDA with a treatment that is twice as complex and expensive, including not only a device but also pharmaceutical agents (drugs), is simply not done absent very strong reasons. In this case, the combinations resulted in remissions of tumors in patients with terminal cancers that were refractory to all other treatments. In no way could this have been predicted. The examiner's attention in this regard is drawn to the examples in the application. Enclosed with this response is a Declaration by Dr. Lentz detailing the treatment of another patient by removal of the soluble cytokine receptor inhibitors. The results are truly amazing and simply could not have been predicted, nor therefore the treatment made obvious from the prior art.

Allowance of all claims 1-29, as amended, and new claims 30-32, is therefore earnestly solicited. All claims 1-32 as pending upon entry of this amendment are attached in an appendix to facilitate the examiner's review.

Respectfully submitted,

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Dated: June 14, 2000
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Certificate of Mailing under 37 CFR 1.8(a)

I hereby certify that this Amendment, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: June 14, 2000

Jean Hicks